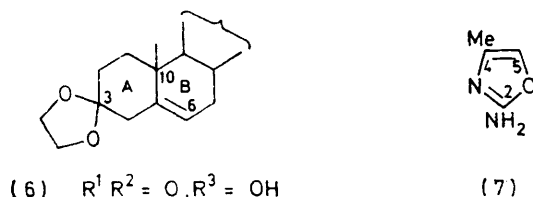
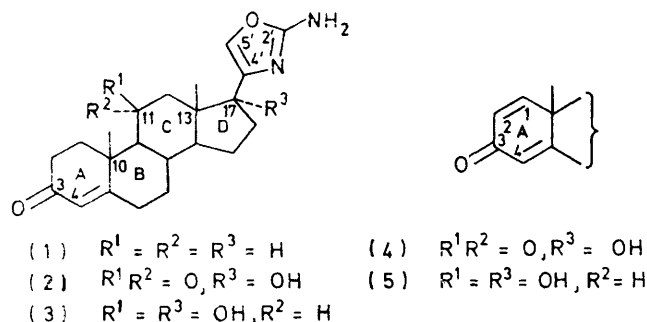


Synthesis of 17 β -(2-Amino-oxazol-4-yl)-steroids

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The reaction of cyanamide with the 20-oxo-21-hydroxy-side-chain of corticosteroids in methanolic aqueous ammonia yields the title compounds.

PREVIOUS attempts to obtain 17 β -(amino-oxazolyl)-steroids, by reaction carried with cyanamide in acidic medium,¹ or, for example from 21-iodocortisone with urea in dimethylformamide,² have failed; however we



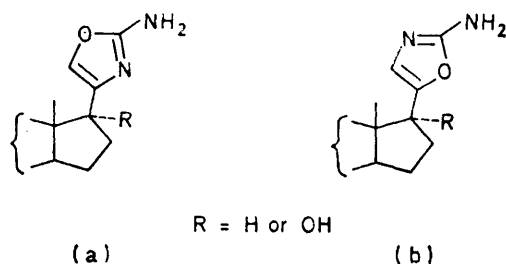
have obtained good results by applying the reaction with cyanamide, but in the presence of ammonia, to steroids with a 17-(α -ketol) side-chain. Sanchez *et al.*³ have recently applied this reaction to some pentoses, but obtained only 2-amino-oxazoline derivatives. From cortexone, cortisone, cortisol, prednisone, prednisolone, and cortisone 3-ethylene acetal we obtained the 17 β -(2-amino-oxazol-4-yl)androstane derivatives (1)–(6), respectively.

The simple 2-amino-4-methyl oxazole (7), which has been a useful model for interpreting the i.r. and ¹H n.m.r. data of compounds (1)–(6), was recently synthesised from cyanamide and hydroxyacetone in aqueous media (as an oil, b.p. 79–81° at 2 mmHg; no spectroscopic data were reported);⁴ we prepared it both by the litera-

ture method and under our own conditions as a solid, m.p. 28–29°, preservable under nitrogen and purifiable by sublimation.

The amino-oxazoles (1)–(6) were identified by their analytical and spectral data. The i.r. spectra (KBr) showed complex patterns owing to strong hydrogen bonding (high m.p.s), but in solution spectra (CHCl₃) the amino-group stretching frequencies were easily identified (*ca.* 3 510 and 3 415 cm⁻¹). Hence as in other 2-amino-oxazole derivatives^{1,5} the amino-form predominates. 2-Amino-4-methyloxazole (7) also shows maxima at 1 643, 1 615, and 1 574 cm⁻¹ which can be assigned to NH₂ scissoring and two ring modes, highly mixed;^{1,6} in the spectra of compounds (1)–(6) the C-20 carbonyl stretching frequency of the parent steroids⁷ is absent and new bands closely similar to those of (7) appear in the 1 645–1 570 cm⁻¹ range (CHCl₃). The 1 640 cm⁻¹ absorption, not well resolved from the C-3 carbonyl stretching band, appears as a very strong band in the spectrum of the 3-acetal (6).

Conversion into the amino-oxazolyl derivatives is invariably accompanied by a negative shift in optical rotation. The reaction only occurs when the 20-oxo-21-hydroxy-side-chain is present; 17 α -hydroxypregn-4-ene-3,20-dione (17 α -hydroxypregesterone), lacking a 21-hydroxy-group, does not react. One might expect that the resulting 17 β -amino-oxazole ring could be 4- or 5-substituted⁸ [(a) or (b)]; however the crude



derivatives do not appear to be isomeric mixtures. T.l.c. shows only one spot, which gives a reddish colour,

¹ W. Loop, H. J. May, and H. Baganz, *Chem. Ber.*, 1969, **102**, 230.

² R. Gompper and O. Christmann, *Chem. Ber.*, 1959, **92**, 1944; R. Lakhan and B. Ternai, *Adv. Heterocyclic Chem.*, 1974, **17**, 99.

³ R. A. Sanchez and L. E. Orgel, *J. Mol. Biol.*, 1970, **47**, 531; D. H. Shannahoff and R. A. Sanchez, *J. Org. Chem.*, 1973, **38**, 593.

⁴ G. Crank and M. J. Foulis, *J. Medicin. Chem.*, 1971, **14**, 1075.

⁵ J. Schuart, H. K. Müller, and U. Wendt, *Pharmazie*, 1974, **29**, 100.

⁶ H. Najer, R. Giudicelli, and J. Menin, *Bull. Soc. chim. France*, 1960, 2052; A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 1961, **12**, 51; A. R. Katritzky and A. J. Boulton, *Spectrochim. Acta*, 1961, **17**, 238; A. Zecchina, E. Borello, and A. Appiano, *ibid.*, 1967, **23A**, 1335.

⁷ W. Neudert and H. Röpke, 'Atlas of Steroid Spectra,' Springer-Verlag, Berlin, Heidelberg, and New York, 1965.

⁸ V. Wolf, P. Hauschildt, and W. Loop, *Chem. Ber.*, 1962, **95**, 2419.

characteristic of the heterocyclic ring, with 2,6-dichlorobenzoquinone *N*-chloroimide (a blue colour is observed for oxazoline derivatives);³ and in the ¹H n.m.r. spectra of the isolated compounds the integrated resonance of the signal assigned to the oxazole ring hydrogen agrees exactly with one proton. The problem of attributing structure (a) or (b) to our compounds was solved by the n.m.r. data (Table).

¹H N.m.r. data (τ values; Me₄Si internal standard) *

Compound (1)	Proton(s) 5'-H	(CD ₃) ₂ SO 3.05 (s)	CF ₃ ·CO ₂ H † 2.92 (s)	CDCl ₃ 3.20 (d, <i>J</i> 0.9 Hz) ‡ 5.0br (s)
(2)	2'-NH ₂	3.73 (s)	2.75br (s)	
	5'-H	2.92 (s)	2.78 (s)	
	2'-NH ₂	3.65 (s)	2.55br (s)	
(3)	5'-H	2.98 (s)	2.76 (s)	
	2'-NH ₂	3.72 (s)	2.6br (s)	
(4)	5'-H	2.91 (s)	2.78 (s)	
	2'-NH ₂	3.64 (s)	2.53br (s)	
(5)	5'-H	2.95 (s)	2.79 (s)	
	2'-NH ₂	3.68 (s)	2.55br (s)	
(6)	5'-H	2.94 (s)		
	2'-NH ₂	3.67 (s)		
(7)	5-H	3.01	2.95	3.17
		(q, <i>J</i> 1.4 Hz)	(q, <i>J</i> 1.4 Hz)	(q, <i>J</i> 1.4 Hz)
	4-CH ₃	8.14	7.80	8.00
		(d, <i>J</i> 1.4 Hz)	(d, <i>J</i> 1.4 Hz)	(d, <i>J</i> 1.4 Hz)
	2-NH ₂	3.6 (s)	2.7br (s)	4.8br (s)

* All the compounds show the expected data for the non-side-chain protons (ref. 7). † In our spectra, the (3)N⁺H resonance was detectable only for compound (1) as a very broad signal at τ -0.3 (the solvent signal covers the range τ -0.5 to -2). ‡ Coupled with 17 α -H.

The 5-H signal of the model oxazole (7) (CDCl₃) lies at almost the same τ value as that of the 5'-H in (1), whereas the 4-H resonance in benzyl 5-methyloxazol-2-ylcarbamate occurs at τ 3.60 in the same solvent;⁹ the paramagnetic shift of 0.40–0.43 p.p.m. is due to deshielding by the vicinal nuclear oxygen.^{1,10} Compounds (2)–(6) are not soluble enough in CDCl₃ for a useful comparison, but this is possible in (CD₃)₂SO; in this solvent, the 5-H signal for (7) lies at τ 3.01 and the 5'-H signal for (1) at τ 3.05; for compounds (2)–(6) this signal, in the same solvent, is found at τ 2.91–2.98. This small paramagnetic shift from the value for (1) is probably due to the effect of the neighbouring 17 α -OH, present in all the latter compounds.

Further, conclusive data supporting structure (a), come from the spectra in trifluoroacetic acid: the 4-H resonance of 2-cyanoamino-5-methyloxazole lies at τ 2.45, whereas the 5-H signal of the 4-methyl isomer is at τ 2.72 (ref. 3), and that of (7) occurs at τ 2.95 in the same solvent. This the 4-H resonance in oxazoles and amino-oxazoles shifts more to lower field than that of the 5-H because protonation always occurs on the ring nitrogen atom.^{1,9–11} In our steroidal derivatives the

oxazole proton signal in CF₃·CO₂H is only in accord with its location at C-5'.

EXPERIMENTAL

Unless otherwise stated, compounds (1)–(6) were prepared by heating the corresponding steroid (2 g) dissolved in methanolic 3.2% ammonia (100 ml) (from aqueous 32% ammonia)¹² with cyanamide (2 mol. equiv.; Fluka; stabilised with 2% boric acid), at 40–45 °C for *ca.* 1 h, under nitrogen with stirring. Products were obtained by concentration under a reduced pressure and were washed with cold methanol and ether. I.r. spectra (CHCl₃ solutions) were recorded with a Perkin-Elmer 457 spectrometer (1 mm cells). Compounds (4) and (5) are not very soluble in chloroform; hence the frequencies of amino-group stretching and of the less intense nuclear mode were not very accurately determined. Absorptions due to the steroidal nucleus occurred at the expected values.^{7,12} [α]_D Values (dioxan) were measured with a Perkin-Elmer 141 Polarimeter. ¹H N.m.r. spectra were recorded with a Hitachi-Perkin-Elmer R-20B apparatus. T.l.c. was carried out on Merck silica gel 60 F₂₅₄ (0.25 mm thick) in chloroform-methanol (3 : 1 v/v); compounds (6) and (7) were revealed by spraying with 1% ethanolic 2,6-dichlorobenzoquinone *N*-chloroimide.

17 β -(2-Amino-oxazol-4-yl)androst-4-en-3-one (1).—The solution obtained from reaction of cortisone was left overnight at *ca.* 5 °C. The product was obtained by evaporation (1.09 g, 50.8%) and recrystallised from ethanol-water (1 : 2); m.p. 259–261° (decomp.), [α]_D 122° (*c* 0.24) (Found: C, 74.35; H, 8.75; N, 7.9. C₂₂H₃₀N₂O₂ requires C, 74.55; H, 8.55; N, 7.9%); ν_{\max} 3 508 and 3 413 (NH₂ str.), and 1 640, 1 601, and 1 572 cm⁻¹ (NH₂ scissor and ω).

17 β -(2-Amino-oxazol-4-yl)-17 α -hydroxyandrost-4-ene-3,11-dione (2).—From cortisone we obtained 1 g (46.9%) of crude product; a sample was purified by dissolving it in boiling absolute ethanol, under nitrogen, and collecting the precipitate formed on concentration under diminished pressure; m.p. 312–315° (decomp.), [α]_D 161° (*c* 0.16) (Found: C, 68.7; H, 7.15; N, 7.4. C₂₂H₂₈N₂O₄ requires C, 68.75; H, 7.35; N, 7.3%); ν_{\max} 3 512 and 3 417 (NH₂ str.), and 1 644, 1 604, and 1 572 cm⁻¹ (NH₂ scissor and ω).

17 β -(2-Amino-oxazol-4-yl)-11 β ,17 α -dihydroxyandrost-4-en-3-one (3).—The solution obtained from reaction of cortisol (30 min) was evaporated to dryness and the solid was treated with cold methanol and washed with ether to give a pale yellow powder (1.115 g, 52.3%). A sample purified as for (2) gave a solid, m.p. 289–291° (decomp.), [α]_D 107° (*c* 0.11) (Found: C, 68.05; H, 8.0; N, 7.0. C₂₂H₃₀N₂O₄ requires C, 68.35; H, 7.8; N, 7.25%); ν_{\max} 3 510 and 3 415 (NH₂ str.), and 1 645, 1 605, 1 573 cm⁻¹ (NH₂ scissor and ω).

17 β -(2-Amino-oxazol-4-yl)-17 α -hydroxyandrost-1,4-diene-3,11-dione (4).—From reaction of prednisone, at 45–47 °C, we collected a crystalline product (0.768 g, 36%), m.p. 308–311° (decomp.) (from absolute ethanol), [α]_D 147° (*c* 0.11) (Found: C, 69.0; H, 7.0; N, 7.15. C₂₂H₂₈N₂O₄ requires C, 69.1; H, 6.85; N, 7.3%); ν_{\max} *ca.* 3 500 and 3 400 (NH₂ str.), and 1 645, 1 602, and *ca.* 1 570 cm⁻¹ (NH₂ scissor and ω).

¹² C. N. R. Rao, 'Chemical Applications of Infrared Spectroscopy,' Academic Press, New York and London, 1963, p. 410.

¹³ H. J. Dauben, jun., B. Löken, and H. J. Ringold, *J. Amer. Chem. Soc.*, 1954, **76**, 1359.

⁹ C. Tanaka and H. Shibakawa, *Yakugaku Zasshi*, 1971, **91**, 425.

¹⁰ H. A. Staab, H. Irngartinger, A. Mannschreck, and M.-T. Wu, *Annalen*, 1966, **695**, 55.

¹¹ A. Katritzky and M. Lagowski, 'Heterocyclic Chemistry,' Methuen, London, and Wiley, New York, 1960, p. 233.

17 β -(2-Amino-oxazol-4-yl)-11 β ,17 α -dihydroxyandrosta-1,4-dien-3-one (5).—From reaction of prednisolone, after 3 h, we collected a pale yellow crystalline *product* (1.1 g, 51.5%), m.p. 271—272° (decomp.) (from absolute ethanol) [α]_D 74° (*c* 0.18) (Found: C, 68.95; H, 7.5; N, 7.25. C₂₂H₂₈N₂O₄ requires C, 68.75; H, 7.35; N, 7.3%); ν_{\max} *ca.* 3 500 and 3 400 (NH₂ str.), and 1 644, 1 604, and *ca.* 1 570 cm⁻¹ (NH₂ scissor and ω).

17 β -(2-Amino-oxazol-4-yl)-3,3-ethylenedioxy-17 α -hydroxy-androst-5-en-11-one (6).—From reaction of cortisone 3-ethylene acetal,¹³ at 47—49°, evaporation to dryness left a residue which was extracted with tetrahydrofuran (distilled from sodium), and 3 volumes of petroleum (b.p. 40—70°) were added causing a yellow oil to separate. This procedure was repeated (total *ca.* 150 ml of tetrahydrofuran) and the residual oil was discarded. The clear solution was evaporated to yield a pale yellow *solid* (1.61 g, 76%), giving needles (from ethanol), m.p. 224—226° (decomp.), [α]_D -14° (*c* 0.67) (Found: C, 67.1; H, 7.6; N, 6.5. C₂₄H₃₂N₂O₅ requires C, 67.25; H, 7.55; N, 6.55%); ν_{\max} 3 510 and

3 418 (NH₂ str.), and 1 643, 1 603, and 1 571 cm⁻¹ (NH₂ scissor and ω).

2-Amino-4-methyloxazole (7).—To an aqueous solution (50%) of hydroxyacetone (6 g, 5.6 ml; 40.5 mmol) in methanol (400 ml) were added 32% ammonia (40 ml) and cyanamide (3.40 g, 81 mmol). The solution was kept for 3 h at 33—38 °C then for 1 h at room temperature. Evaporation *in vacuum* to *ca.* 30 ml was followed by extraction with methylene chloride (200 ml). The extract was washed twice with water, dried (Na₂SO₄), and evaporated to leave a pale yellow oil that crystallised at 20 °C (1.7 g, 42.8%). The *product* was collected as a solid condensing in a sublimator cooled at 0 °C (0.05 mmHg); resublimation yielded colourless crystals, m.p. 28—29° (under nitrogen) (Found: C, 48.65; H, 6.2; N, 28.3. C₄H₆N₂O requires C, 48.95; H, 6.15; N, 28.55%); ν_{\max} 3 510 and 3 415 (NH₂ str.), and 1 643, 1 615, and 1 574 cm⁻¹ (NH₂ scissor and ω). A sample prepared by the method of Crank⁴ was identical (analytical and spectroscopic properties).

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